Comments on steroidal contraception

A report of the meeting of the International Planned Parenthood Federation Central Medical Committee and its advisers held in New York on 11 and 12 April 1970 to discuss the known and postulated side-effects of steroidal contraception

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INTERNATIONAL PLANNED PARENTHOOD FEDERATION

COMMENTS ON STEROIDAL CONTRACEPTION

A report of the meeting of the International Planned Parenthood Federation Central Medical Committee and its advisers, held in New York on 11 and 12 April 1970 to discuss the known and postulated side-effects of steroidal contraception.

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CONTENTS

PREFACE

Steroidal contraceptives are widely used and constitute an effective method of contraception. Like many innovations in medicine they carry with them certain risks. Some of these are unpredictable and cannot be proved not to occur in advance of widespread use.

More than twenty million women throughout the world are now planning or limiting their families by means of steroidal contraception, mainly in the form of oral contraceptives. As experience has grown, a number of side-effects have been discovered. These side-effects can be slight and of little consequence, or they can be severe, even causing death in exceptional cases.

The possible hazards of all active pharmacological substances and their various combinations must be investigated, especially those used on a large scale, such as steroidal contraceptives. The logical possibility exists that evidence might accumulate to suggest that some or all of these drugs should be withdrawn from use. At the same time a balance must be maintained in publishing substantiated or unsubstantiated reports of serious hazards. Harm has been done in recent times, not least to the peace of mind of the women who use these substances, by rumours and perhaps by exaggerations of their potential hazards that often spread with alarming rapidity through the mass media.

It was with all this in mind that the Central Medical Committee of the International Planned Parenthood Federation, acting on a suggestion from the Western Hemisphere Regional Medical Committee, called a conference in New York on 11 and 12 April 1970. This conference was attended by the Central Medical Committee, its panel of experts on steroidal contraception, and a group of authoritative international observers. The conference concentrated on the more serious actual and postulated side-effects of steroidal contraception, such as thromboembolic disease. Less attention was paid to the common, but far less serious side-effects, such as nausea.

The aims of the conference were three-fold: (1) to inform the member associations of the IPPF and doctors working in those countries of what is known about the possible hazards and to make some suggestions about their clinical implications; (2) to provide comprehensive and dispassionate information about the situation to the medical profession at large; and (3) to produce authoritative information for the public health services and governments with which the IPPF cooperates in the field of contraception.

This publication is a distillation of the discussion that took place at this conference,* together with other relevant information that has come to the Central

* The conference had before it a draft paper prepared by Dr Malcolm Potts, the Medical Director of the IPPF, reviewing the adverse reactions and possible long-term hazards of steroidal contraceptives.

Medical Committee's notice since the time of the meeting. As far as possible, only general principles are dealt with, and should be applicable for some time to come. To avoid confusion, commercial preparations are not mentioned by their trade names, since these differ in different countries.

Each actual or possible hazard of steroidal contraception is listed separately; in each case the particular problem is posed, the known facts about it are assembled, and the clinical implications of the available data are discussed. There is also an overall evaluation of steroidal contraceptives, and an attempt is made to compare the known and potential hazards of their use with the risks of non-use or use of alternative methods of contraception.

When the conference in New York ended, the Central Medical Committee prepared a statement based on the discussions that were held. This was published in the April 1970 issue of the *IPPF Medical Bulletin* and is reproduced in Appendix A on page 43.

Appendix B on page 47 contains a selected bibliography of a number of important publications on the side-effects of steroidal contraception. Some of these are source papers substantiating statements made in the text, some provide details of side-effects that for reasons of space could not be covered in the present publication, and some review the particular topic under discussion.

The IPPF Central Medical Committee takes full and sole responsibility for the contents of this publication.

INTRODUCTION

The possibility of hormonal contraception was suggested in 1919, but this only became a reality in the late 1950s with the work of Pincus, Rock, Chang and others in developing oral contraceptives. During the 1960s oral contraceptives were used on an increasingly large scale in many countries. More recently, the variety of steroidal contraceptives has increased; injectable hormones have been used in many clinical trials, and the use of implanted steroidal contraceptives, and once-a-month and post-coital preparations is being explored. To date no significant clinical progress has been made in developing steroidal contraceptives for men.

Types of steroidal contraceptives

Combined preparations

These were the first oral contraceptives to be introduced, and contain a progestagen and an oestrogen, given in constant proportions and amounts for 20, 21 or 22 days, followed by an interval without medication during which uterine bleeding occurs. The most common regimen is to use the 21-day preparation followed by an interval of seven days when either no tablets are taken or placebo, iron or vitamin tablets are substituted.

Combined preparations act by diminution in the output of pituitary gonadotrophins which lead to an inhibition of ovulation. In addition, they may interrupt fertility as a result of changes in the ovary, tubes, cervical mucus and endometrium.

Sequential preparations

In sequentials, oestrogen is given alone for 14 to 16 days, followed by a combined tablet containing an oestrogen and a progestagen for 5 to 7 days. These are again followed by an interval without tablets or with a placebo. Sequential preparations also alter gonadotrophin secretion, but have less effect on the cervical mucus, endometrium, and other target organs.

Continuous-dose progestagens

The daily use of 0·5 mg. or less of one of a variety of progestagens can regulate fertility without inhibiting ovulation. Gonadotrophin secretion is not altered as much as with combined or sequential preparations, but antifertility changes in sperm capacitation, the cervical mucus, the endometrium, and ovarian and tubal function, may be relatively more important.

Once-a-month preparations

A long-acting oestrogen, which is stored in the body fat and slowly released, is used in combination with a short-acting progestagen and is given in a single

tablet at a precise time in the menstrual cycle. These preparations are at the clinical trial stage.

Injectable hormones

Exogenous hormones may be given by injection as well as orally. Depot preparations of progestagens are given to last one, three or six months.

Implants

Silastic capsules containing progestagens can be implanted subcutaneously or intramuscularly or placed in the vagina or uterus from where the hormone is absorbed. Prolonged, continuous release of steroid, giving a satisfactory contraceptive effect for six to 12 months, has been obtained in limited clinical trials. With technical modifications it may be possible to extend this interval. Unencapsulated implants of pure steroid and of lipid/steroid mixtures are also being explored.

Post-coital preparations

Oestrogens have been used clinically in the first week after exposure to pregnancy in an attempt to prevent implantation.

Change in dosage

The range of steroids used in systemic contraceptives is widening and there is a tendency for the dose of both progestagen and oestrogen to be reduced.

Usage

It is thought that more than 20 million women now use oral contraceptives. In developed countries, at worst, one in 20 of those taking oral contraceptives give up their use every month, and at best three out of five persist in taking them for more than two years. The duration of use rises with age and social class and varies in different ethnic groups. Almost as many women have taken oral contraceptives in the past as use them at present. On the evidence of past experience, use in developed countries may rise by 50 to 100% in the next decade. A very much greater potential for expanded use exists in many developing nations.

Clinical and epidemiological observations

It is known that the various possible methods of hormonal contraception do not all have comparable actions. The rare adverse side-effects considered in this publication mainly apply to the use of oral contraceptives and are based on the experience which has been gained with the use of combined and sequential preparations. They do not necessarily apply to injectables, implants, once-a-month or postcoital preparations. It should be recognized that until any method of contraception is used on a very wide scale, involving many hundreds of thousands, or possibly millions of people, it is impossible to determine and measure the frequency of side-effects. In the future development of steroidal contraception, new hazards, which are unpredictable, could possibly arise.

However, the methodology which is being used to investigate and evaluate the adverse side-effects of current oral contraceptives is relevant to other steroidal forms of contraception which may be introduced.

Oral contraceptives are made from synthetically produced analogues of ovarian hormones. The oral dose given represents a greater quantity of hormones than is produced in the normal menstrual cycle, but less than that which circulates in the later stages of pregnancy. Variations in hormone dose and particle size can occur in manufacture. Knowledge is fragmentary concerning the quantity of the hormones absorbed from the gastrointestinal tract, their transport, distribution in different tissues and metabolism. It is not known whether the drug given or a metabolite is active at the cellular and subcellular level. Different steroids and different doses of the same steroid may have different actions and different points of attack.

There may be significant variations in the transport, metabolism and action of contraceptive steroids in humans and in animals used for pharmacological evaluation.

Oral contraceptives produce a number of physiological changes in the women taking them, and some of the possible reactions have been studied, using biochemical and physiological tests. Most of the studies involve relatively small groups of women, and base-line and control data have not always been included.

Clinical observations on relatively small groups of patients have provided considerable information concerning immediate, common, usually minor side-effects. However, common symptoms, occurring in association with a widely used drug, are difficult to measure, and the similar incidence of side-effects in oral contraceptive and intra-uterine device users demonstrates the need for creating adequate control groups and eliminating unwanted variables. It is necessary to allow for the fact that oral contraceptive use may be correlated with other factors, such as coital frequency, sexual hygiene, smoking, etc., which have a proven effect on certain diseases. Double-blind trials using a placebo are rarely possible in the field of contraception, but double-blind trials using two or more formulations of oral contraceptives are possible and should be carried out more frequently.

Prospective studies

Small groups of oral contraceptive users have been followed up for several years. Three prospective studies, each involving between 10,000 and 25,000 oral contraceptive users and an equal number of controls, have been planned, but to date no large-scale prospective study has been concluded. The size of the groups of controls and users required in prospective studies is determined by the incidence of the disease under consideration in the control groups, the assumed change in the incidence of the disease consequent on the use of oral contraceptives, the length of time for which the study is planned to run, and the degree of statistical significance intended.

For instance, at a statistical significance level of 0·05, a fairly accurate estimate has been made of the smallest samples of oral contraceptive users and of controls needed to detect a doubling of various disease rates in the oral contraceptive

users in a prospective study lasting one year. The incidence of cancer of the breast in 10,000 women, aged between 20 and 45 years, in the normal population in one year is 2-2, and 85,000 oral contraceptive users and 85,000 controls would be needed to detect a doubling of the disease in the users. In the same way, cancer of the body of the uterus has an annual incidence of 0 3 per 10,000 normal women, aged between 20 and 45 years; 600,000 users and 600,000 controls would be needed in a prospective study to show the disease had doubled in incidence. In the case of diabetes, where there is an incidence of 20 per 10,000 per year, only 9,000 users and 9,000 controls would be needed to show doubling, and where neonatal malformations are being looked for, with an incidence of 300 per 10,000 per year, only 600 infants in each group are needed. In all cases the women entering the prospective study would have to be followed-up for a full year, with all the difficulties implicit in the large numbers required.

A study running for 10 years requires only a quarter to a third as many users and controls as one running for a year, but the difficulties of keeping thousands of women under review for 10 years would be immense, apart from the fact that many oral contraceptive users would discontinue the method to start a pregnancy or for other reasons.

Retrospective studies

The technique of retrospective studies, using the case-control method, is more practical and has already been used in the case of thromboembolism and oral contraceptives. The number of cases needed to achieve a statistically significant result is determined by the proportion of women in the population who are using the method of contraception and does not depend on the incidence of the disease under investigation.

Thus, at a statistical significance level of 0 05, if a quarter of all the women in a population have ever used the method, only 120 cases of the disease and 120 controls are needed to detect a doubling of the disease rate because of the use of oral contraceptives. Where half the population have used the method, only 110 cases and 110 controls are needed.

Retrospective studies also have built-in difficulties. There may be a bias in diagnosis between users and controls because of a doctor's awareness of a suspected correlation between a disease and the use of steroidal contraception. Also, it is not always easy to determine the number of users of steroidal contraception in the population from which the case-control sample has been drawn.

These epidemiological observations have been given in some detail to show the difficulties faced by scientific workers in attempting to arrive at a true estimate of the incidence of side-effects caused by steroidal contraceptives. In the discussions summarized in this publication this fact should constantly be borne in mind.

THROMBOEMBOLISM

The problem

From 1961 onwards reports have been published of venous thrombosis, pulmonary embolism, cerebral thrombosis and coronary thrombosis among women from developed countries taking oral contraceptives. Gestagens, in particular oestrogens, have been shown to affect certain of the elements concerned in the mechanism of fibrin formation and fibrinolysis. The complete sequence of events which takes place in thrombosis has not been entirely elucidated.

The available facts

In 1967 a case-control, retrospective study organized by the Royal College of General Practitioners in Britain concluded that there was a relationship between thromboembolic disease and the use of oral contraceptives, although at that stage it proved impossible to measure the size of the risk.

In a later study, women aged between 16 and 40 years admitted with thromboembolic disease to a number of large hospitals in Britain during the years 1964 to 1967 were investigated; and in another survey reports of all deaths from thromboembolism which had taken place in women aged 20 to 44 years in Britain during 1966 were carefully looked into. The results of these investigations were published in 1968. More recently (1969) similar studies were carried out in the USA, and the British surveys have been continued.

The evidence from these studies demonstrates a statistically significant relationship between the use of oral contraceptives and the development of venous thrombosis and pulmonary embolism, as well as the development of cerebral and coronary thrombosis. Women over 35 years of age are at greater risk than younger women (Table I). The risk of development of thromboembolic disease does not appear to be related to the duration of use of oral contraceptives.

All these case-control retrospective studies were carefully designed to eliminate

TABLE I. ANNUAL MORBIDITY AND MORTALITY RATES PER 100,000 USERS AND NON-USERS OF ORAL CONTRACEPTIVES IN GREAT BRITAIN

	Age in years	*Oral contraceptives*	
		Users	*Non-users*
Morbidity (general practice)*	15–49	450	130
Morbidity (hospital admissions)†	16–40	50	6
Mortality†	20–34	1·5	0·2
Mortality†	35–44	3·9	0·5

* Venous thromboembolism (predominantly superficial thrombophlebitis)
† Venous thromboembolism (deep-vein thrombosis and pulmonary embolism) and cerebral thrombosis.

biases such as those which might have arisen owing to a readiness by doctors to diagnose thromboembolic conditions in women known to be using oral contraceptives. The findings from the USA and Britain confirm one another in most respects. While certain aspects of the retrospective studies conducted to date can be criticized, on the basis of probabilities their findings are widely accepted as applying to the women of developed countries.

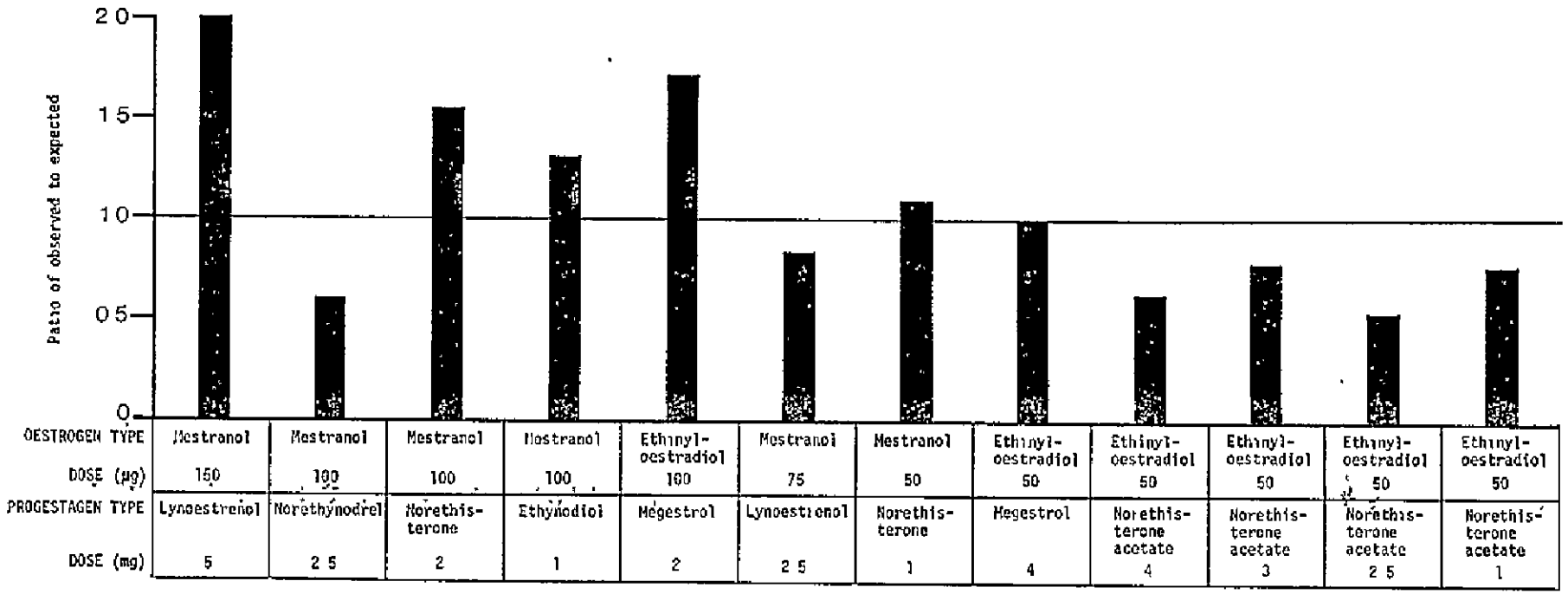
Information on the relationship between the content of oestrogen in combined oral contraceptives and the occurrence of thromboembolic disease became available from Britain and Scandinavia in April 1970. This was based on an analysis of reports of thromboembolic disease received by national drug registration authorities (such as the Committee on Safety of Drugs) in Britain, Sweden and Denmark, which were compared with the number of similar adverse reactions predicted from market-research estimates of oral contraceptive sales, assuming that all products carried the same risk. It was found that the actual number of reports exceeded the predicted number for most preparations containing more than 75 μg. of oestrogen. Therefore it was concluded that preparations with a low dose of oestrogen present least risk of thromboembolic disease, and in Britain the cautious recommendation was made that, wherever possible, combined oral contraceptives containing 50 μg. of oestrogen should be used. Certain individual products do not appear to fit into the general pattern found of excess or lower risk according to the amount of oestrogen they contain. The reports about individual products vary in number, and these anomalies do not all have the same statistical significance (Fig. 1).

To date, epidemiological studies have not been able to demonstrate if there are any other factors determining the risk of thromboembolic disease. One study has suggested that sequential preparations carry a greater risk than combined ones, but this has not been confirmed. No significant differences have been detected between the two oestrogens used in all combined oral contraceptives (ethinyloestradiol and mestranol), although they are known to have different biological potencies in other respects. Certain progestagens are known to be partially metabolized to oestrogens. Variations in manufacture, intestinal absorption and metabolism may be important, but it has not been possible to allow for them.

Evidence is now becoming available to demonstrate that women who undergo surgical operations while using oral contraceptives have a slightly higher risk of postoperative thrombosis. A recent British study in a group of 30 women with thromboembolism and in 60 matched controls showed the risk to be increased threefold to fourfold by the use of oral contraceptives.

In view of the widespread awareness of thrombotic episodes associated with the use of oral contraceptives, it is likely that women with bad varicose veins or with a past history of thrombosis use this type of contraception less often than other women. To date, no quantitative data are available to determine if the risk from using oral contraceptives in such cases is raised, but cases of repeated thrombosis following use, discontinuation of use and re-use have been reported.

In addition to the epidemiological evidence of the relationship between the use of oral contraceptives and thromboembolic phenomena, there are physiological and biological data which provide further circumstantial evidence of the



OESTROGEN TYPE	Mestranol	Mestranol	Mestranol	Mestranol	Ethinyl-oestradiol	Mestranol	Mestranol	Ethinyl-oestradiol	Ethinyl-oestradiol	Ethinyl-oestradiol	Ethinyl-oestradiol	Ethinyl-oestradiol
DOSE (μg)	150	100	100	100	100	75	50	50	50	50	50	50
PROGESTAGEN TYPE	Lynoestrenol	Norethynodrel	Norethis-terone	Ethynodiol	Megestrol	Lynoestrenol	Norethis-terone	Megestrol	Norethis-terone acetate	Norethis-terone acetate	Norethis-terone acetate	Norethis-terone acetate
DOSE (mg)	5	2 5	2	1	2	2 5	1	4	4	3	2 5	1

Fig. 1. Ratio of observed number of reports of total thromboses, including arterial, to number expected on the basis of sales of products with the oestrogen/progestagen formulations shown.

(Fig. 1 is based on a diagram included in the statement of the British Committee on Safety of Drugs in the *British Medical Journal* of 25 April 1970, and is used here by permission of the Committee on Safety of Drugs and the Editor of the *British Medical Journal*.)

validity of the relationship. Following the work on oral contraceptives, it was shown that the use of oestrogens to suppress lactation raised the incidence of puerperal thromboembolism in treated women. Large doses of oestrogens used in the treatment of male diseases, such as cancer of the prostate, are associated with an increased incidence of thromboembolism in men. It has been possible to show changes in certain of the clotting factors, as well as in some aspects of vascular physiology, in women using oral contraceptives. Histological changes in the intima of the blood vessels of women taking oral contraceptives have been reported in a single study.

The incidence of thromboembolic disease, in the absence of steroidal contraception, shows marked geographical variation, both inside and outside developed regions. It is not known if this is due to ethnic or environmental differences. It is the impression of many observers that thromboembolic disease is especially rare in most developing countries.

It is not known if the risk which has been measured in Britain and the USA is an addition to the basal rate of thromboembolic disease in these countries, or if it is a multiplier of that basal rate. In a community where there is a low basal incidence of thromboembolic disease and if the use of oral contraceptives were to cause an addition to this risk, such a community would experience an appreciable increment in the risk of thromboembolic disease caused by oral contraceptives, but the total incidence would be lower than that in Britain or the USA. Alternatively, if the use of oral contraceptives is a multiplying factor, then in a community with an extremely low basal rate of thromboembolism, the risk from oral contraceptives would be very substantially lower than in Britain or the USA.

No studies have been carried out in the field of thromboembolic disease and oral contraceptive use either in developing countries or in predominantly non-Caucasian women. Retrospective studies of the relationship between thromboembolic disease and oral contraceptive use in developing countries would be very difficult indeed to undertake, while prospective studies require a level of social and medical organization which is only found in Britain, Scandinavia and the USA. Consideration should be given to the possibility of studying the incidence of postoperative, postpartum or other types of thrombosis in certain developing countries.

In a small group of women (22) of fertile age with myocardial infarction, 50% were found to be using oral contraceptives. Nearly all the women, whether using oral contraceptives or not, had an independent predisposing risk of developing ischaemic heart disease, such as hypertension, hyperlipidaemia, or excessive smoking, although none had any carbohydrate intolerance. It is possible that oral contraceptives only contribute to the risk of myocardial infarction in those otherwise prone to the disease.

Thromboembolic death from any cause is relatively rare among women in the fertile years. The risk involved in oral contraceptive users and the number of women using oral contraceptives may be expected to give rise to a measurable change in the national registration of deaths from this cause. In Britain and the USA there has been a rise in the number of deaths due to thromboembolic disease in both men and women. However, in the opinion of most observers, the trend

in female deaths due to this condition is compatible with the increase in the use of oral contraceptives.

Bleeding tendencies in human beings are known to be related to the blood group system. One study has indicated that the risk of venous thromboembolism is lower in women of blood group O than in women of blood groups A, B or AB. A possible increased incidence of thromboembolism in women taking oral contraceptives and who suffer from sickle-cell anaemia is discussed on page 39.

Clinical implications

The risk of death or morbidity following the occurrence of thromboembolic phenomena among women taking oral contraceptives is compatible with the continued use of these preparations, since the risks attendant on the increased likelihood of pregnancy following non-use outweigh the risks of use in nearly all circumstances. It is not thought that the relationship of blood groups to the tendency to clotting changes is of sufficient practical use to be important in deciding whether to give or withhold oral contraceptives. There is no other predictive test that will identify women who may be at particular risk.

The risk of thrombosis is generally held to be increased by slowing of the circulation, a rise in blood coagulation factors, and by damage or alteration to the vessel walls. No predisposing cause of thrombosis is universally accepted as an absolute contraindication to the use of oral contraceptives. Some predisposing causes are relative contraindications in certain circumstances.

In some countries manufacturers are obliged to insert information in packages of oral contraceptives concerning possible predisposing conditions to thrombosis and other rare adverse side-effects. Such package inserts may be aimed at doctors and/or users of the oral contraceptives.

Doctors or paramedical workers dealing with individuals, and administrations with responsibility for populations of women, must exercise commonsense and as much caution as is compatible with the circumstances in which they find themselves. It is necessary to avoid, at the one extreme, the position that a possible relative contraindication, because it is unproven, should be dismissed from consideration, and, at the other extreme, the position that, unless a possible contraindication can be proved to be irrelevant, steroidal contraceptives should not be given to women with that condition.

When circumstances permit, and if alternative effective methods of family planning are available to potential users, it is prudent to deny the use of steroidal contraceptives to women with a diagnosis of: (*a*) previous thrombosis, (*b*) severe heart disease, or (*c*) certain blood dyscrasias, such as leukaemia or polycythaemia.

It is wise to substitute an alternative method of contraception six weeks before major elective surgery and during the immediate postoperative period.

If any of the following symptoms appear in any women taking oral contraceptives, their continued use should be carefully assessed: (*a*) cramps, pain or oedema in the legs, (*b*) sudden severe migraine or unusual headache, (*c*) sudden onset of severe chest pain, or (*d*) visual disturbances. The use of oral contraceptives in the presence of certain chronic diseases is discussed on page 39.

Steroidal contraceptives which do not contain oestrogens may carry no risk of thrombosis, and the relative contraindications noted above probably do not apply to this group of contraceptives.

Where combined oral contraceptives are used, those with a low dose of oestrogen are recommended whenever possible. However, it is recognized that a certain number of women may develop breakthrough bleeding with low-dose preparations, and it is to be emphasized that it remains responsible practice to give women, when necessary, formulations containing higher doses of oestrogen.

As has been noted, it remains an open question whether the data on thromboembolism from Britain, the USA, Sweden and Denmark can be extrapolated to other parts of the world, especially to regions where the incidence of thromboembolic disease appears to be rare. However, until more evidence is available, in situations where other methods of effective contraception can be substituted, it may be wise to exercise caution where there are relative contraindications.

CANCER

The problem

Both the level of circulating ovarian hormones and the balance between the various components are very likely to differ in a woman taking steroidal contraceptives from what is found in a woman with a normal menstrual cycle. Cancer is a disease which develops slowly, and the pattern of hormonal experience early in reproductive life may influence the incidence of the condition in later years. Many substances known to cause cancer in man do not produce a clinical effect for 10 years or more.

Cancer is a complex but poorly understood subject, and as long as we remain ignorant of the cause and control of malignant disease it is impossible to predict, with certainty, the effect of exogenous steroids on the incidence of cancer from purely laboratory observations. In addition to the practical difficulties of designing satisfactory laboratory experiments, it is not known if exogenous ovarian hormones might exert an effect of themselves, or as a result of suppressing endogenous ovarian function. It is also not known whether any potential effect would have to be regarded as a threshold effect or one that was linearly related to dose (the bigger the dose the bigger the effect). There is also no agreement whether any potential effect might act through initiating a malignant process or by potentiating other carcinogens. All these unsolved problems could lead to profoundly different interpretations of any laboratory or clinical observations.

Long-term animal tests are necessary, and in progress, but a large number of variables have to be taken into account in evaluating the results of animal experiments. For instance, the following criteria are among those which are important in setting up experiments to investigate the long-term effects of steroidal contraceptives; the type and dose of the exogenous hormone, the duration of treatment, the rate and route of administration, the preparation of the drug and the type of vehicle used to administer it, whether the exogenous hormone is given continuously or cyclically, and the balance between oestrogens and progestagens and between oestrone and oestradiol.

In choosing an experimental animal, the age, sex, stage of fertile life, type of reproductive cycle, number of pregnancies before and after treatment, frequency of lactation, the genetic or strain constitution, the environment and presence or absence of carcinogens (such as a 'milk factor'), the response of the endogenous hormone system, the metabolic pathways for ovarian hormones, the nature of circulating metabolites, and the organ clearance of the steroids are all important factors. Control groups of animals also have to be kept.

Epidemiological evidence, of necessity, must be slow to accumulate. Geographical differences may be significant. The nature of the problem whether steroidal contraceptives affect cancer does not have a definitive solution at the present stage of clinical use and observation of these agents. The available data can be used, however, to infer whether or not it is responsible practice to use

steroidal contraceptives at all and to focus attention on the type of selection care and follow-up which should be given to women using this method of contraception.

In theory, steroidal contraceptives could lower the incidence of malignancy in any organ, they could raise the incidence, or they could have no effect one way or the other. It is also theoretically possible that they could have opposite effects in different organ systems at the same time. The variations in the oestrogens and the progestagens used in combined oral contraceptives, as well as the absolute dose and the relative proportions, could be relevant to the problem.

The available facts

The relationship between hormone environment and cancer can be studied by tissue culture technique, but to date no useful *in vitro* screening test for potential carcinogens has been developed.

Possible relationships between ovarian hormones and cancer have been studied in animals. All gestagens used in steroidal contraceptives have been submitted to prolonged testing in two or more mammalian species. Oestrogens, administered in relatively high continuous doses, have been associated with the development of cancer in rats, mice, hamsters, rabbits, and dogs, but not in guinea pigs, cows, pigs, or monkeys. In breast cancer of some strains of mice, oestrogens appear to be essential for the effect of the 'milk factor' and of carcinogenic hydrocarbons. In order to demonstrate a carcinogenic action for oestrogens in rats and mice, the pituitary gland must be intact. Prolonged administration of certain synthetic oestrogens, in doses relatively greater than those used for contraceptive purposes in women, has been associated with the development of breast tumours in bitches. In 16 out of 48 beagle bitches, aged 18–29 months, the administration of chlormadinone (6-chloro-6-dehydro-17α-acetoxyprogesterone), also in relatively high doses, was associated with the development of breast nodules. Most lesions were benign, but one tumour was variously regarded as 'premalignant' or 'malignant'. Breast conditions of this type are also seen in untreated beagle bitches, but not at the age of these animals.

As outlined above under 'The problem', difficulties in extrapolating data from one species to another are formidable. For example, pregnancy early in human reproductive life protects against breast cancer, while in some strains of mice pregnancy raises the incidence of this form of cancer, and in others it only occurs during pregnancy. The little that is known about the metabolism of steroids in various species indicates that important differences exist, in particular between the dog and several other species. Additional comparative metabolic studies are needed, and if carried out might allow a more rational selection of experimental animals for testing steroidal contraceptives than is possible at present. It seems unwise to make decisions concerning the use of a steroid because of adverse findings in one species; equally, the need for vigilance in the human field should not be discarded because of the negative findings in primates or other species.

Ovarian hormones have been used therapeutically for more than 35 years, and synthetic gestagens were introduced in 1938. When groups of women have been surveyed no increase in breast, endometrial, cervical or ovarian cancer has been

demonstrated in association with the use of oestrogens for therapeutic reasons, and evidence of a lowered incidence has actually been claimed. However, only approximately 2,500 women have been followed up (the duration of follow-up varying between three months and 25 years), and in most cases the women were over 40, so that these data are of little or no positive value. Cases of breast carcinoma have been found in some men after treatment of prostatic cancer with high doses of oestrogen, although the lesions have also been reported as prostatic metastases. Breast cancer has also been reported in two transsexual men after the use of oestrogen.

Very few cases of malignancy have been found among women taking part in clinical trials of oral contraceptives. Equally, few cases of cancer among women using oral contraceptives have been notified to governmental drug registration authorities, although such reporting may reflect medical interest as much as a representative sampling of events. Statistics from a number of developed countries, with a high use of oral contraceptives, have shown no significant change in the mortality and morbidity from breast cancer in the past decade, and a definite decline in the number of deaths from cervical carcinoma in the same period. The value to be placed on this negative evidence depends partly on whether the potential effect being investigated is considered to be the initiation of a process or the potentiation of a process which is basically dependent on other than endocrine factors. If the effect is an initiation one, it could be argued that the duration of useful clinical experience with oral contraceptives falls short of the latent period of possible adverse carcinogenic reactions—in other words, that they have not been used long enough to produce actual carcinoma. If the possible effect were a potentiation of carcinogenic factors then it could be argued that the negative evidence to date is of greater significance.

General biological and clinical considerations direct attention towards cancer of the breast, cervix and endometrium.

Breast

It is not known in detail if, or how, the pathological processes which precede clinically detectable breast neoplasia are influenced by steroid hormones, although they are known to be slow to develop. On balance, the hormone environment seems important. Cancer of the breast is rarely found before puberty, and pregnancy (especially before the age of 20) seems to have a protective effect. Ovariectomy between the ages of 20 and 40 also seems to be protective, but to have no influence after the age of 40. No cases of cancer of the breast were found in the published records of 85 women under the age of 40 who had been treated with oestrogens therapeutically for an average of five years, but this small series is of little statistical value.

Established breast cancer can respond in different ways to steroids. Ovariectomy leads to remission in up to half the cases of premenopausal breast cancer. Gestagens have been used in the treatment of breast cancer.

There is no evidence that the use of oral contraceptives has been associated with any change in the incidence of breast cancer, but greatly extended studies (probably of a retrospective type) are required. Two cases of cancer of the

breast have been found in 2,000 women using injectable contraceptives for six years, but the numbers involved are too small to draw useful conclusions.

Cervix

Cervical cancer is a neoplasm of the epithelium. It has many of the characteristics of a contagious disease transmitted by sexual intercourse, being almost unknown in virgins, but relatively common in those who begin intercourse early, have frequent intercourse and/or several sexual partners. A type II herpes virus has been implicated in some studies. Barrier methods of contraception may give some protection against the disease.

The cytology of the cervix shows characteristic changes with various hormonal states, but no clear correlation between the endocrine environment and cancer of the cervix has been established in man. An atypical endocervical hyperplasia has been described in a small group of patients using oral contraceptives. It is a benign condition and nearly always asymptomatic, although its full significance has not been determined. Somewhat similar changes have been found in pregnancy.

The use of Papanicolaou smears is thought by nearly all workers to provide a valuable diagnostic tool for predicting the subsequent development of cervical cancer. It is thought that there is a time relationship of about 10–15 years between the appearance of abnormal cytological findings and invasive carcinoma.

Papanicolaou smears have been widely used in preventive medicine in developed countries, especially in women beginning or continuing to use oral contraceptives. A number of short-term studies of Papanicolaou smears in oral contraceptive users, involving a total of over 10,000 women, have been published. However, the incidence of abnormal smears varies in different populations and it has been difficult to construct the necessary series of carefully matched controls. In addition, women with abnormal smears are usually treated, removing those at risk from the population of oral contraceptive users.

Some series have claimed a decline in prevalence of abnormal smears among oral contraceptive users, but a raised prevalence was found in one USA study. In this study more than 6,000 oral contraceptive users, of a year's duration or more, were matched with nearly 4,000 diaphragm users for five variables of : age, parity, age at first pregnancy, income and ethnic group. The prevalence of lesions diagnosed as carcinoma *in situ* was higher in women who had used oral contraceptives than in diaphragm users, but the prevalence did not rise with time. A raised prevalence rate has also been found in one smaller, less well-controlled British study. A number of explanations of the results are possible: the matching of the control group may have been inadequate; the barrier method may protect against abnormal changes; oral contraceptive users may have more frequent intercourse, leading to a higher incidence of abnormal changes; errors may arise during the difficult and subjective task of interpreting cytological and biopsy changes under the microscope; and finally there may be a direct correlation between oral contraceptive usage and abnormal smears. However, neither the authors nor the United States Food and Drug Administration interpreted the changes as indicative of a causal relationship between oral contraceptives and pathological cervical conditions. Further studies are now taking place.

Endometrium

Endometrial (adenomatous) hyperplasia is thought by some to be more common in women who, for pathological or therapeutic reasons, have a high level of circulating oestrogens. It has been suggested, but not proved, that such hyperplasia is a precancerous condition preceding by several years the development of endometrial neoplasia.

Endometrial hyperplasia, and in some cases carcinoma of the endometrium, regresses with high doses of progestagens. The endometrium of a woman receiving combined oral contraceptives shows poor glandular development, and after several cycles of use may become relatively atrophic. A decidual reaction is sometimes found.

Clinical implications

The nature of the problem is such that it is impossible, at the present time, to prove whether steroidal contraceptives are with or without a risk of carcinogenesis, or whether they may be protective against malignant disease. In view of the variety of organs which may be affected, the latent period in the development of cancer and precancerous conditions, and the current biological ignorance about many aspects of neoplasia, it is unlikely that the total picture of the problem will be filled in for many years. It is also very unlikely that any single observation will provide a definitive answer to the problem posed by the use of steroidal contraceptives. It should be noted that several of these problems are shared by the numerous new biologically active substances which are being added to the human environment at present.

The extent and limitations of valid and constructive systems of clinical care, both at the communal and individual level, must be determined in the light of the available data. At the communal level further attempts should be made to measure the incidence of cancer and precancerous conditions among users of steroidal contraceptives and among controlled groups of non-users. Doctors engaged in well-planned, carefully conducted prospective studies of the possible relationship between the use of steroidal contraceptives and a raised or lowered incidence of cancer should attempt to the utmost of their ability to follow up and record the progress of patients as carefully as possible.

Retrospective studies will probably prove more practical than prospective studies (see page 9). It is likely that the availability of medical skills, the presence of adequate systems of mortality and morbidity registration and the scale of use of steroidal contraceptives will determine that most studies will take place in developed countries, although even here cooperation between several nations may be necessary At the same time it must be remembered that the incidence of some malignant conditions, such as breast cancer, shows wide geographical variations.

General pathological considerations, as set out above, direct particular attention towards the study of cancer of the breast, endometrium and cervix. Cancer of the breast is probably the most important disease to be studied and may also be the one which, for technical reasons, is most amenable to investigation by the case-control method.

At the individual level prudence requires that, whenever possible, caution must be exercised on behalf of the users of steroidal contraceptives, but, equally, frankness demands recognition of the fact that at present very few practical steps can be taken to reduce any risk to the individual that may exist.

Women with precancerous conditions or established neoplastic disease, if there are medical facilities for their identification and treatment, require special care, and an individual clinical decision has to be made about the type of contraceptive method to be used, which may or may not involve the use of steroidal contraceptives. In situations where oral contraceptives are freely available, the risk of exacerbating undiagnosed malignant conditions in potential users should be balanced against the risk of pregnancy, which can also exacerbate malignant disease.

The carrying out of routine physical examinations of the pelvis and breasts, and the taking of Papanicolaou smears when distributing steroidal contraceptives, is sound preventive medicine. However, the availability of these services is not a prerequisite for prescribing or making available steroidal contraceptives. In the absence of positive evidence concerning an association between abnormal cervical cytology and the use of steroidal contraceptives, the need for a cervical cytology service should be judged from the point of view of the overall needs of preventive medicine. If facilities for taking Papanicolaou smears are limited, it is probably useful to use them first in those situations where there is epidemiological evidence of an increased risk of cervical cancer (such as in those women who start regular sexual intercourse early in life or who belong to poor socio-economic groups) than in those oral contraceptive users where the evidence neither confirms nor refutes a possible relationship with cancer of the cervix. This does not of course apply where special epidemiological studies are being carried out

It is likely that different countries or geographical areas will find it necessary to establish their own base-line data concerning the incidence of abnormal cervical cytological findings. Pilot cytological project studies on women using and not using steroidal contraceptives may be required in several different countries or regions.

GENETIC CHANGES

The problem

The first chromosome reduction division in the primary oocyte takes place before birth in the human female. The second reduction division and the formation of the first polar body occur shortly before ovulation. This chromosomal reduction and the sequence of changes which takes place at fertilization, the process of cleavage, implantation and embryonic development could occur in an abnormal hormonal environment in the case of a woman who became pregnant while using steroidal contraceptives, who started steroidal contraceptives after fertilization had taken place, or who deliberately misused oral contraceptives in an attempt to interrupt a pregnancy. In theory steroidal contraceptives could also have an adverse effect on development by interfering with the rate of tubal transport or by alterations in the uterine environment.

It is known that in certain mammals the level and type of circulating sex hormones can (during a crucial few days of late fetal development) imprint a pattern of neuro-endocrine behaviour on the hypothalamus. It is suspected that this occurs in a number of other mammals as well. Under certain conditions individuals with a female genotype can be made to follow a male pattern of behaviour, which only becomes apparent when the individual animal reaches mature fertile life.

The available facts

In doses comparable with those given to women, the ovarian hormones used in currently available steroidal contraceptives have not proved teratogenic in animals. Large doses of certain steroids in *in vitro* studies have been shown to have an effect on chromosomal division in certain cell lines. The same effect has not been demonstrated *in vivo*.

Follow-up of babies born to women who have used steroidal contraception has not shown any statistically significant change in the incidence of congenital abnormalities, nor has there been any increase in congenital abnormalities reported in those countries (like Sweden) with a high standard of medical surveillance, and a large number of women using oral contraceptives.

Published follow-up series are all of less than 500 cases, and it must be remembered that an ideal study of a possible increase in the incidence of congenital abnormalities should involve 10,000 babies with a five-year or longer follow-up. In addition to noting congenital abnormalities, such a study should include the frequency of twins and the sex ratio of births.

Steroidal contraceptives are very effective in preventing pregnancy, but a small number of women do begin or continue to use this method early in pregnancy. The virilization of female fetuses has been reported with high doses (10 mg. or more) of norsteroids given in the treatment of threatened abortion, but this complication has not been recorded with oral contraceptives currently in use.

Clinical implications

Although it seems self-evident, women should be told to stop using oral contraceptives completely when they want to become pregnant, and equally, they should be clearly instructed not to continue using oral contraceptives if they think they are pregnant. They should be careful always to begin the use of oral contraceptives in the first week following the beginning of menstruation, and they should be deterred from the improper (and pointless) attempt to use large doses of oral contraceptives as a supposed abortifacient.

Injectable depot progestagens have a prolonged action. Pregnancy might occur before the effect of the exogenous hormones has completely worn off, but there is no evidence of harm to the fetus of such a pregnancy.

Follow-up studies on children born to women who have used steroidal contraceptives are necessary, but the proportion of women giving up the use of these contraceptives to begin a wanted pregnancy is relatively small, and any worthwhile prospective study is only likely to be undertaken at a large centre or by a large organization.

CHANGES IN SUBSEQUENT FERTILITY

The problem

Biologically, steroidal contraceptives might have an adverse effect on subsequent fertility by affecting the pituitary-ovarian axis (see pituitary, page 26). Prolonged use of steroidal contraceptives might also have an adverse effect on the ovaries or on the uterus, affecting its ability to accept an implanting blastocyst and/or sustain a developing pregnancy.

The available facts

There is no satisfactory epidemiological evidence about the prevalence of anovulatory menstrual cycles in otherwise healthy women. Surveys have been conducted into the return of ovulation following the prolonged use of steroidal contraceptives. The evidence from prospective studies involving several hundred women suggests that there may be a slight delay in ovulation immediately after stopping combined or sequential oral contraceptives, but that there is no significant overall difference in the length of time which it takes to achieve pregnancy if women are matched for age.

When oral or injectable contraceptives are being used, the ovaries are small and biopsies show surface fibrosis, but these changes are similar to those found in pregnancy and are reversible.

There is an impression that cannot at present be confirmed or refuted that in a very small group of women a prolonged interval of anovulation can occur after discontinuing the use of combined or sequential oral contraceptives. Meaningful studies are difficult to construct because allowance has to be made for increasing age, and many of the women involved may not have proved their fertility before taking oral contraceptives. In women complaining of infertility following the cessation of oral contraception, endogenous oestrogen production is low and serum luteinizing hormone levels are in the low normal range, but the ovaries respond to exogenous gonadotrophins and to clomiphene. Sometimes these women have galactorrhoea.

The disturbance in ovulation is thought to be hypothalamic, and it is possible, but not proven, that combined and sequential oral contraceptives may have different effects. Spontaneous cure is common, and as far as is known virtually all cases respond to clomiphene. The woman's history, before the initiation of steroidal contraception, is commonly one of irregular menstruation, suggesting frequent anovulatory cycles. The history may also be of juvenile metropathia, but a history of regular cycles does not exclude the possibility of a delay in the return of ovulation.

When injectable contraceptives are used, there can be a marked delay in the return of fertility, and persistent anovulation is known. The simplest explanation would be that depot preparations take some time to be eliminated from the body, although alternative explanations involving target organs, like the cervical mucus, must be considered, and infertility seems to last longer than anovulation.

Clinical implications

Nulliparous women beginning oral contraception should know that fertility cannot be proved in advance of attempting to become pregnant. Young nulliparous girls present a particular problem, and oral contraceptives should be used with caution in those with a history of irregular menstrual cycles. At the same time, it must be recognized that in some countries it is necessary to prescribe oral contraceptives to protect young girls against unwanted pregnancies, which can present a serious hazard to health.

Until more information is available about injectable preparations, it is probably wise to avoid giving them to nulliparous women, and it is still not known if the duration of their use should be limited.

In the past, recommendations were made to discontinue the use of oral contraceptives after first two and then four years of use. These recommendations were based on administrative rather than scientific considerations. It is not known if the length of use of oral contraceptives has any effect on the chances of successful treatment in cases of persistent anovulation, and, to date, there are no valid data to justify interruption of the use of oral contraceptives at arbitrary intervals in order to determine if ovulation will occur.

Treatment with clomiphene in women with prolonged anovulation following the use of oral contraceptives has been encouraging.

PITUITARY CHANGES

The problem

Combined oral contraceptives inhibit ovulation as the result of alterations in the release of pituitary hormones. Animal experiments demonstrate that circulating ovarian hormones have an action on the pituitary gland itself, on the hypothalamic control of pituitary releasing factors and on other brain centres.

The long-term control of the menstrual cycle and the mechanisms which influence the onset of puberty and the menopause are not understood, and caution is required in predicting the effect of synthetic hormones on the complex mechanisms involved.

The available facts

The two ovarian hormones act differently and the dose and type of combination are also important. There is no evidence that the partial suppression of cyclical pituitary function which accompanies pregnancy is deleterious, even if repeated many times during fertile life.

The morphology of the pituitary gland in women using steroidal contraceptives is practically unknown and, for obvious reasons, large-scale studies will always be impossible. In a small series of monkeys, given oral contraceptives over relatively brief intervals, no change in pituitary histology or weight has been observed and no constant change has been found in the pituitary glands of those laboratory animals which have been investigated.

Clinical implications

Pituitary disease is rare in fertile women and no routine clinical precautions are necessary when giving oral contraceptives to individual women. It has been the practice of some physicians to discontinue medication for a brief interval every two years or so, but there is no evidence that such a procedure is beneficial (see also page 25).

CHANGES IN LACTATION

The problem

The pubertal development of the mammary glands and their response to pregnancy and lactation are influenced by ovarian and pituitary hormones and by thyroid, parathyroid and pancreatic endocrine secretions. The endocrine control of lactation itself is still incompletely understood. Oestrogen has a generally inhibitory influence on the mammary glands. The influence exogenous ovarian hormones have on lactation itself may differ according to whether they are given before, during or after the establishment of lactation.

In developing countries most babies are totally dependent on an adequate supply of breast milk. Lactation is also an important factor in extending the interval between pregnancies in many parts of the world.

The available facts

There is conflicting evidence about the effect of combined oral contraceptives on lactation. It has been claimed that these agents have no significant effect on lactation, and this may be largely true of low-dosage combined oral contraceptives given to Western women after lactation has been established. However, carefully conducted trials in Egypt, with adequate controls, demonstrate a slight reduction in the milk volume, a moderate change in its constituents, and a possible shortening of the time of weaning with a combined preparation, although no profound change in infant growth has been noted.

Progestagens alone by mouth have no effect on lactation, while further studies in Egypt and other parts of the world show that the use of injectable progestagens is associated with a raised milk yield and a small but measurable increase in protein and lactose.

Although traces of exogenous steroids are excreted in the mother's milk, no harmful effects have been noted in breast-fed babies of mothers using steroidal contraceptives. High peaks of circulating hormone may occur in women on depot injections, and further research into this aspect of the problem is required.

Clinical implications

In developed countries breast feeding and the use of low-dosage combined oral contraceptives are compatible, since a slight reduction in milk volume would not be harmful to the baby. However, in developing countries additional caution is needed in the use of combined oral contraceptives so that lactation is not interfered with. Depot medroxyprogesterone acetate has been shown to be of great value in stimulating lactation quite apart from its contraceptive action. It has also been demonstrated that intra-uterine devices are unusually well tolerated during lactation.

It must be remembered that lactation is only a partial form of contraception and that conception commonly occurs during the later part of unprotected lactation especially if menstruation has been re-established. A new pregnancy itself has a demonstrably adverse effect on lactation. Therefore some form of adequate contraception needs to be started early—not later than the third month after delivery if lactation is well established.

METABOLIC CHANGES

The problem

Glucose tolerance alters with the menstrual cycle and is lowered in pregnancy; that is, the glucose tolerance curve shows a raised serum glucose. A variety of additional metabolic changes are known to take place in response to alterations in the hormonal environment. There are differences in the incidence of certain diseases in the two sexes (e.g. cardiovascular conditions) which can be ascribed to differences in the hormonal environment and to the changes consequent on this.

The available facts

The effect of exogenous and endogenous steroids on metabolism has been studied in several species of laboratory animals. Also, several detailed analyses of human metabolic responses to the use of oral contraceptives have been carried out in small groups of women. Sometimes the subjects studied were selected because of clinical evidence of an adverse response to oral contraceptives or because of a history of diabetes, and control groups of subjects have often been inadequate. There is no predictive test to show which women might have an altered biochemistry when taking steroidal contraceptives. No evidence from the woman's history can be correlated with the biochemical changes found; nor do these biochemical changes correlate with the clinical symptomatology.

Several studies have shown that women on oral contraceptives have a reduced glucose tolerance. There is no evidence that this change alters with the duration of use. Very little is known about the pathogenesis of diabetes, and it cannot as yet be confirmed or refuted that these biochemical changes bear any relationship to the eventual development of frank diabetes.

The following additional biochemical alterations have been reported by various workers in response to the use of oral contraceptives. They are not all equally significant, and some observations remain to be confirmed:

hypertriglyceridaemia
hyperinsulinism
raised human growth hormone secretion
hyperpyruvataemia
hyperphospholipidaemia
raised serum copper, iron and zinc, and iron-binding capacity
raised α_2 macroglobulin, transferrin, albumin, immunoglobulin G, cryofibrinogen, transcortin, and free unconjugated cortisol.

Some changes, for example those in the plasma triglycerides, which are moved towards the male pattern, might only prove significant after long-term use of steroidal contraceptives. These changes return to normal on discontinuation of therapy. Prospective studies which may throw light on this problem are now taking place.

The effect of different steroidal contraceptives and varying dosages may be significant. Continuous low-dose progestagens and injectable contraceptives may have fewer metabolic reactions than combined oral contraceptives, but further observations are needed. It is possible that further research will bring formulations to light that will eliminate some of the changes that have so far been observed.

Clinical implications

Oral contraceptives can be given to women with established diabetes, but extra care in observation and diabetic control is needed during the first one or two months of oral contraceptive use. There is as yet no information whether the use of oral contraceptives in diabetes is related in any way to the development of peripheral vascular complications. However, some doctors do recommend non-steroidal methods of contraception in frank diabetes, but it should be remembered that pregnancy in a diabetic woman presents a particular hazard.

There is evidence that sequential preparations have less effect on glucose metabolism than combined oral contraceptives, and that low-dose progestagens have the least effect of all oral contraceptives.

It is hoped that further work will be done on all aspects of the metabolic changes associated with the use of steroidal contraceptives. However, in the absence of sound epidemiological studies, of a simple predictive test concerning which women are likely to have possible adverse reactions, and of a clearer understanding of the possible long-term consequences of observed changes, no routine clinical measures can be taken by, or on behalf of, the individual woman.

LIVER DAMAGE

The problem

Recurrent idiopathic jaundice of pregnancy (benign recurrent cholestatic jaundice of pregnancy) is thought to be a response to a change in hormonal environment. Steroids, and in particular the 17-alpha-alkyl-substituted steroids, are known to cause alterations in liver function and cholestasis.

Clinical reports of jaundice in women using oral contraceptives have appeared in Britain and the USA, but especially in Scandinavia. The sequence of clinical events in many of these cases, in particular the cessation of jaundice when medication is withdrawn (and occasionally the reappearance of the condition when oral contraceptives are used again), provides powerful evidence of a causal relationship between the use of oral contraceptives and possible liver damage.

As the liver is involved in numerous metabolic activities, and in the detoxication of various drugs, changes in liver function overlap with certain other effects of oral contraceptives.

The available facts

More than 200 cases of jaundice among users of oral contraceptives have been published. No information is available to determine the exact incidence of such adverse reactions, although nation-wide reports of jaundice to the Swedish Committee for Adverse Drug Reactions suggest that jaundice occurs in one in 4,000 users in that country. Half of all cases occur within four months of beginning use. No large-scale studies have been conducted to show whether the pattern of case reports reflects a genuine ethnic difference in susceptibility. Susceptibility to jaundice in connection with oral contraceptives may be hereditary.

Liver function has been studied in small groups of women using oral contraceptives. A variety of liver function tests have been used and not all studies are comparable. The number of patients involved in many studies is insufficient to allow generalization.

Bromsulphthalein excretion (BSP) is mildly impaired in up to 40% of women using oral contraceptives—an alteration which may partly result from a reduction in serum albumin concentration. Other changes in empirical liver function tests have also been reported.

Abnormal liver function reverts to normal within a few weeks of cessation of use of oral contraceptives in nearly all cases, and no evidence of long-term liver damage has been published.

Ultrastructural changes in liver parenchyma cells have been described. It has been suggested that the effect of oral contraceptives on liver cells is to alter permeability rather than cause damage to cell organelles.

Clinical implications

It is unwise to give oral contraceptives to women with a history of idiopathic recurrent jaundice of pregnancy. Oral contraceptives should also be withheld from those with a history of chronic idiopathic jaundice (Dubin-Johnson and Rotor syndromes) or recurrent generalized pruritus of pregnancy.

Women with abnormal liver function, as after viral hepatitis, should not be given oral contraceptives until the liver function tests have returned to normal. In areas where medical surveillance is difficult, and a good deal of self-medication may take place, it is possible that some women with poor liver function may begin oral contraception. It is unlikely that they would continue if they became jaundiced, and the risk of long-term illness appears small. It should be emphasized on all occasions that women who develop itching or jaundice or who pass dark urine should stop taking oral contraceptives.

HYPERTENSION

The problem

Changes in blood pressure during pregnancy are wholly or partly due to alterations in blood volume, cardiac output and the mechanical effects of placental and uterine enlargement; it is not known in detail how the endocrine alterations of pregnancy affect the cardiovascular system. There is some elevation of plasma renin, and plasma angiotensinogen levels are increased in response to oestrogen.

Cases of hypertension accompanying the use of oral contraceptives have been reported, and the sequence of events in some of the published cases is presumptive evidence for a causal relationship.

The available facts

Exogenous steroids are associated with secondary changes in aldosterone output and reactivity to renin but these changes occur in women who have no clinical rise in blood pressure when using oral contraceptives, as well as in those who show a rise in blood pressure.

One published epidemiological study involved 1,575 users and non-users of oral contraceptives and showed a very slight increase in blood pressure in users (120·4 to 122·7 mm. Hg adjusted for height, weight and arm circumference). The change did not increase significantly with the duration of medication.

The use of certain progestins may be associated with sodium retention and may have an anabolic effect; oestrogens can be associated with water retention and oedema. Nevertheless oral contraceptives have been given to small groups of women with congestive cardiac failure, essential hypertension and hypertension consequent to chronic nephritis without apparent worsening of these conditions.

Clinical implications

The possibility of a rare idiosyncratic response to oral contraceptives should be recognized and medication discontinued if symptoms of hypertension occur and the condition is confirmed by examination. The effect of ovarian hormones on fluid balance should be kept in mind, but hypertension does not appear to be an absolute contraindication to the use of oral contraceptives.

Where facilities exist a record of blood pressure before the use of oral contraceptives is useful, especially in women of 35 or over, and is also good preventive medicine. However, the limitations of a single recording of blood pressure should be recognized. The use of a blood pressure record as a prerequisite of oral contraceptive distribution, and subsequent checks during use, should be judged in the context of the health needs of the community and the available medical and paramedical resources.

OBESITY

The problem

Women using steroidal contraceptives sometimes complain of weight gain. Oestrogens can lead to fluid retention and progestagens can have an anabolic effect.

The available facts

Satisfactory studies, involving a significant population of women and with adequate controls, have not been carried out.

Progestins can have an anabolic effect, but weight gain, when it occurs, is mainly due to fluid retention, greater food intake and/or less physical activity on the part of the women. The mechanism leading to increased appetite is not understood and might be either a direct effect of the exogenous steroids or the consequence of a relief from stress.

Clinical implications

The known position can be explained to women and it can be emphasized that any weight gain which has taken place will respond to reduction in food intake and, especially, limitation of sodium intake.

DEPRESSION

The problem

Short-term changes of mood in women of fertile age can sometimes be correlated with phases of the menstrual cycle: it is well established that in some women episodes of depression occur premenstrually and during menstruation, while quantitative changes have been demonstrated at these times in intellectual performance, working ability, accident rates, hospital admissions (for a variety of causes), and even criminal acts.

The syndrome of postpartum depression is well recognized, as is the fact that the menopause is correlated with a variety of psychiatric conditions.

In all psychical changes mentioned above, a link with the woman's endocrine background is very likely. Psychotic episodes have also been reported in association with the use of high doses of ovarian hormones in the treatment of endometriosis. When investigating the problem of a possible association between steroidal contraceptives and episodes of depression, a distinction must be made between giving these preparations to women who are already manifestly depressive patients, and finding depression as a new symptom in women taking steroidal contraceptives.

The use of steroidal contraceptives could be related to the occurrence of mild changes of mood or to more severe psychiatric conditions. By causing changes of mood, these agents could also have beneficial effects and might relieve certain psychiatric complaints.

The available facts

It is exceptionally difficult to make objective observations on this question. One study claims to demonstrate that the incidence of depression is the same among women with intra-uterine devices as among those taking oral contraceptives. Quantitative assessments are difficult both because depression is awkward to measure and because satisfactory control groups of non-users (or information about preceding segments in the life of the woman before the use of contraceptives) are not easy to establish. The use of placebos is difficult. However, when one takes all these factors into account, it still seems likely that in rare cases the use of combined oral contraceptives can be associated with episodes of depression.

Psychotic episodes do not appear to occur more often in women who have suffered emotional disturbances in the past, before using steroidal contraceptives.

There is reasonable evidence that the use of steroidal contraceptives relieves the premenstrual syndrome in many women, as well as asthma related to menstruation.

Clinical implications

It is unlikely that a careful psychiatric evaluation of steroidal contraceptive users (if this were possible on a large scale) would significantly reduce the incidence of adverse psychiatric effects. It may be wise to withdraw the drug if frank depression occurs, although it will remain difficult to establish whether a particular episode of depression was or was not causally related to the use of steroidal contraceptives.

It should be remembered that women with severe psychiatric disorders may well find their ability to cope with daily life markedly reduced by an unwanted pregnancy.

CHANGES IN LIBIDO

The problem

Sexual behaviour in mammals is partly dependent on the level of circulating steroids. There is some evidence in humans that sexual behaviour varies with the menstrual cycle and with pregnancy, although psychogenic factors play an important part as well. Both because of their content of steroids and the change in mood that the freedom from the possibility of pregnancy may bring, the use of steroidal contraceptives may alter libido in women.

The available facts

Oestradiol given to ovariectomized female rhesus monkeys stimulates copulatory activity in their male partners, while progesterone depresses it. Combined preparations have been shown to reduce copulatory behaviour in intact rhesus monkey pairs.

As in the case of depression, assessment of changes in libido is difficult. The relative roles of social, psychological and endocrine factors in human sexual activity are impossible to determine. Overall, most reports indicate an increase in coital frequency in women on oral contraceptives. Whether this is a true increase in libido, or a reduction of inhibition of a normal libido because of freedom from fear of unwanted pregnancy, is not easy to say. It seems likely that a minority of women, whose behaviour is obscured in group surveys, may suffer a genuine reduction in libido on combined preparations.

Clinical implications

There is no known predictive test to identify women whose libido may decrease. If a loss of libido becomes a genuine drawback to the use of combined oral contraceptives in particular women, sequential preparations or alternative methods of contraception should be instituted.

MENOPAUSAL CHANGES

The problem

It has been suggested that prolonged suppression of hypothalamic-pituitary function and the interruption of the normal sequence of maturation and atresia of ovarian follicles might delay the onset of the menopause. The hypothesis has also been put forward that the precipitous withdrawal of exogenous hormones might cause sudden ageing. It is necessary to have a clear understanding of when steroidal contraceptives should be stopped around the time of the menopause.

The available facts

There is no correlation between parity (numerous pregnancies are associated with prolonged intervals of ovarian suppression) and the onset of the menopause, although this is related to socio-economic background and to certain endocrine diseases

There are several million primordial follicles present in the ovaries by the sixth month of intra-uterine life, but most of these are lost by the age of puberty. About 50 or more primordial follicles undergo atresia in each menstrual cycle. The rate of spontaneous follicular atresia appears to be unaffected by the use of steroidal contraception.

Clinical implications

The administration of steroidal contraceptives near the time of the menopause should be regulated by the need for adequate contraception, and the balance between the declining risk of conception with age, the increased risks of each pregnancy, the observed rise in the incidence of thromboembolic disease in oral contraceptive users in this age group (see page 10), and the need to deal with menopausal symptoms.

The use of steroidal contraceptives can induce cyclical regular bleeding beyond the menopause. Mechanical methods of contraception may be substituted at intervals after the age of 45, to determine if spontaneous menstruation will still occur. It is unlikely that steroidal contraceptives will be needed by any woman after the age of 50.

STEROIDAL CONTRACEPTIVES AND CHRONIC DISEASE

The available facts

The use of the available oral contraceptives is not thought to affect adversely the progress of *tuberculosis*, *leprosy* or *malaria*. Limited information is available on the relationship between the use of steroidal contraceptives and *diabetes mellitus* (see page 29). There is no useful information concerning the use of oral contraceptives in populations where glycosuria is relatively common in older age groups in the rice-eating areas of the world.

In mice exceptionally high doses of oestrogens cause generalized liver damage which some evidence shows may be worse in animals infected with *bilharzia*. However, little information is available about the effect of steroidal contraceptives containing oestrogen on women with bilharzia. Some workers believe that the focal nature of the disease makes adverse effects less likely than in women with any form of generalized liver disease.

A relationship between oral contraceptives and certain *endocrine diseases* has been observed, but further information is needed. Oral contraceptives have no effect on normal thyroid function, although they affect the level of protein-bound iodine. They can probably be used in regions of endemic goitre, although clinical surveys would be useful. It is not known how oral contraceptives affect the management of hypo- and hyperthyroidism.

Chronic nutritional hypochromic anaemia is likely to improve with the use of oral contraceptives, as the menstrual loss is reduced and a rise in haemoglobin levels can be demonstrated. The meagre evidence available does not suggest that oral contraceptives have an adverse effect in cases of malnutrition.

Women with sickle cell anaemia (sickle cell trait SS or SC) are believed to be less fertile than normal women Pregnancy may precipitate a sickle cell crisis, but gestagens are thought to extend the interval between sickle cell crises. The use of oral contraceptives in women with sickle cell anaemia appears to be acceptable, but additional information is required on this topic.

Clinical implications

Where adequate facilities are available for the diagnosis and treatment of disease, advice on oral contraceptives can be provided by those medical and paramedical personnel responsible for the health care of the community.

In some areas facilities for the diagnosis and treatment of chronic diseases are inadequate. In such areas the risks of widespread distribution of steroidal contraceptives must be reviewed against the background of making alternative forms of contraceptives available and balanced against the consequences of non-use of contraceptive measures, which would lead to unplanned pregnancies complicating the progress of the chronic disease.

STEROIDAL CONTRACEPTIVES AND OTHER DRUGS

No adverse reactions have been observed when steroidal contraceptives and other types of medication are used together. Chemotherapy for tuberculosis, malaria and schistosomiasis is not thought to be affected by the use of oral contraceptives, although more detailed observations in this field would be valuable.

USE OF MEDICAL MANPOWER

It is recognized that the availability of medical personnel differs widely in different parts of the world. In areas where there is a shortage of doctors, the distribution of steroidal contraceptives by paramedical personnel under medical supervision may free the physician's services for more demanding and urgent tasks.

FUTURE DEVELOPMENTS

It is likely that the pattern of steroidal contraception in use will change slowly and that additional new methods will be introduced. Attempts to widen the range of available contraceptive methods should be encouraged, but it must be recognized that any innovation in steroidal contraception will also include unpredictable hazards that will have to be monitored, measured and evaluated.

National and international regulations and guide-lines for the preclinical testing and clinical use of drugs are necessary. Steroidal contraceptives must be shown to have an exceptionally low level of serious adverse side-effects, because they involve continued use (experience to date suggests they are used, on average, for two to three years, with a minority use over a much longer period).

Regulations governing the use of contraceptive drugs should be sufficiently flexible to permit the introduction of new methods at an optimal time in their development.

Once a contraceptive drug has reached community use, continued monitoring of rare adverse side-effects should be encouraged and supported.

CONCLUSION

The galaxy of interlocking individual and communal pressures which go to create the necessary and humane goal of planned parenthood cannot be summarized here. But one measure of the strength of a woman's individual desire to avoid unwanted pregnancy is the resort to legal and illegal abortion which is found in all countries. In the last analysis the non-clinical factors governing the use of systemic methods of contraception are as important or more important than the health factors.

There is no doubt that steroidal contraceptives have a number of complex effects upon human physiology, some of which are not entirely understood and others which cannot be fully evaluated until these substances have been in use for a longer period and until numerically more significant follow-up studies have been completed.

Steroidal contraceptives give rise to a variety of mild or moderately severe side-effects in a significant number of users, and very rarely serious side-effects can occur.

It is equally well established that for some women oral contraceptives are beneficial and they are, of course, used in the treatment of certain pathological conditions such as metropathia, dysmenorrhoea, the premenstrual syndrome, and endometriosis, and have been used, usually in higher dosages, in the treatment of malignant disease.

Oral contraceptives are the most effective reversible method of family planning available: on average about one woman in 200 will fall pregnant during twelve months' use. Oral contraceptives are several times more effective than barrier methods of family planning, and in developed countries have been adopted mainly by those groups previously using condoms, diaphragms or the rhythm method, but for some couples oral contraception has made the use of contraceptives acceptable for the first time. Some women are emotionally committed to the method and find it aesthetically preferable and more convenient than other forms of contraception. However, it must be emphasized that steroidal contraception is only one of several family planning procedures. Various methods may be applicable under differing circumstances or at different periods throughout a woman's reproductive life.

Oral contraceptives are widely used in many highly developed countries, and have become the most popular method of contraception in the national family planning programmes of two Asian countries. They have a useful place in the family planning services of all nations, and there is no doubt that they have not yet reached all their potential users.

The possible risks of steroidal contraception must be weighed against the undoubted benefits of their use, and in evaluating the suitability of different methods of contraception, their relative effectiveness is significant. The attempt

to balance the risks of unwanted pregnancies against the hazards of contraceptive use is useful, but simple estimates conceal a great many important variables and no assessment should be attempted in very exact terms.

Even in countries with a low maternal mortality, the proven risk of death from thrombosis associated with one year's use of oral contraceptives is only one-tenth of the risk of dying associated with one pregnancy, excluding the risk associated with illegal abortion. Comparison is somewhat difficult, because thromboembolic risk has been measured among women with no predisposing causes, while maternal mortality includes previously healthy women and women with a variety of established illnesses. By coincidence, the risk of death from puerperal phlebitis, thrombosis and embolism after one pregnancy is of the same order as the risk of death following one year's medication with oral contraceptives.

It is certain that the risks from unwanted pregnancies in many developing countries are ten or 20 times as great as in developed countries, and lack of access to family planning methods, including the use of steroidal contraceptives, can prove a serious risk to life.

The future possible, unpredictable hazards of steroidal contraceptives present difficult problems of evaluation. There is no doubt that continued monitoring of possible adverse reactions will be required for a very long time. It is equally clear that, while community studies are essential and will be fruitful, it is exceptionally difficult to protect the individual patient from all elements of risk.

It is recognized that, while any innovation in medicine carries with it risks which are unpredictable, the availability and use of steroidal contraceptives are important in maternal health and in the health of the family. Taking all factors into consideration, the continued use of steroidal contraception is fully justified.

APPENDIX A

IPPF CENTRAL MEDICAL COMMITTEE STATEMENT

Thromboembolism

The evidence of a causal relationship between the use of steroidal contraceptives and thromboembolic disease is accepted. This complication is, however, very rare.

It is agreed that in women with (*a*) a previous history of thrombosis, (*b*) severe heart disease, or (*c*) certain blood dyscrasias, it is prudent to deny the use of steroidal contraceptives if alternative effective methods of family planning are acceptable to potential users.

It is thought wise to substitute an alternative method of contraception six weeks before major elective surgery and during the immediate postoperative period. If any of the following symptoms appear, the advisability of the continued use of steroidal contraception should be carefully assessed: (*a*) cramps, pain or oedema in the legs, (*b*) sudden severe migraine or unusual headache, (*c*) sudden onset of severe chest pain, or (*d*) visual disturbances.

The incidence of thrombotic disease in the absence of steroidal contraception shows marked geographical variation. It is not known if this is due to ethnic or environmental differences. It is the impression of the Committee that in those areas where thrombotic disease is especially rare, women are also less prone to the thromboembolic complications of steroidal contraception.

The recent recommendation by the British Committee on Safety of Drugs (the Scowen Committee) concerning the relationship of oestrogen dosage to the risks of thrombotic disease is accepted as valid. The Medical Committee concurs in recommending the use of oral formulations containing not more than 50 micrograms of oestrogen whenever possible. However, it recognizes that a certain number of women may develop breakthrough bleeding at this dosage, and emphasizes that it remains responsible practice to give women, when necessary, formulations with a higher oestrogen content.

The surveillance of neoplastic disease

In theory, steroidal contraceptives could lower the incidence of malignancy in any organ, they could raise the incidence, or they could be entirely irrelevant. The Committee and its consultants feel that the time interval since the introduction of steroidal contraception is too short to make any definite statement on this subject.

Drawing together the available evidence, they have decided that it remains responsible practice to continue to use steroidal contraceptives. At the same time it is important to monitor the effects of these drugs on statistically significant samples of women.

The use of cervical cytology and routine breast palpation when distributing steroidal contraceptives is sound preventive medicine. It is desirable, but not imperative, to carry out such examinations at regular intervals on steroidal contraceptive users. The availability of such examinations is not a precondition for the distribution of steroidal contraceptives.

The Committee recognizes that research in this area is difficult and at present may only yield incomplete answers. Therefore it welcomes the fact that additional research is taking place in several countries.

Possible fetal abnormalities

To date there is no evidence to suggest that steroidal contraceptives in the dosages currently in use have any adverse effect on children born to mothers who have discontinued their use, who become pregnant during use, or who breast-feed their babies while under medication. The Committee realizes that the available studies are on relatively small numbers of cases, and hopes that further studies will be initiated.

Lactation

There is evidence to suggest that combined and sequential contraceptives, because of their oestrogen content, produce an adverse change in both the quantity and the quality of milk and the duration of lactation. Progestagens alone by mouth have no effect on lactation, while by injection they seem to stimulate the production of milk.

The Committee recognizes that lactation is only a partial form of contraception and it is hazardous to await the appearance of the first postpartum menstrual period before initiating or resuming contraception.

Hypertension

The Committee notes that rare cases of hypertension which appear to be causally related to the use of steroidal contraceptives have been reported. This phenomenon is reversible in most instances. A blood pressure measurement as a precondition for the distribution of steroidal contraceptives, and subsequent checks during use, should be judged in the context of the health facilities of the community.

Jaundice

Rare cases of jaundice in association with the use of steroidal contraceptives have been reported, usually in patients who have had jaundice in previous pregnancies. As far as is known, this condition is always reversible. Steroidal contraceptives should not be given to women with a previous history of idiopathic jaundice of pregnancy.

Previous infectious hepatitis is not a contraindication to steroidal contraception.

Metabolic effects

The Committee agrees that there are alterations in glucose tolerance in certain women using steroidal contraceptives containing oestrogen. These changes are

of a small order of magnitude and are reversible. They may be subject to geographical variation and their significance is undetermined.

There is no evidence that glucose tolerance is further impaired in potential diabetics. It is possible to continue to control diabetes itself while steroidal contraceptives are being used. It is not known whether steroidal contraceptives play any role in the causation or evolution of potential or established diabetes mellitus.

Several observers have reported changes in triglycerides and other blood lipids. These alterations all returned to normal levels with cessation of medication. The long-term significance of such changes cannot be established at the present time.

Subsequent fertility

There is an impression that cannot at present be proved or refuted that in a small group of women a prolonged interval of anovulation occurs after distinuing oral contraceptive use. It is thought that this risk is greater in women with a history of irregular menstruation suggesting anovulatory cycles. The spontaneous cure rate is high and nearly all the women requiring treatment respond satisfactorily.

It is recognized by the Committee that in some countries it is necessary to prescribe oral contraceptives to protect young girls against unwanted pregnancies. There is no necessity or justification for the use of oral contraceptives to regularize menstruation except where contraception is indicated.

There is no need to limit the length of time over which oral contraceptives can be used. There are no valid data to justify interruption in the use of oral contraceptives at arbitrary intervals in order to determine if spontaneous ovulation will occur. Data are still insufficient to evaluate the effect of injectable steroidal contraceptives on subsequent fertility.

Mental changes

Changes in both mood and libido have been reported in users of steroidal contraceptives. These may be advantageous or adverse, and are very difficult to evaluate objectively. It may be wise to substitute an alternative method of family planning in women with disturbing changes in mood or libido.

General observations

It became clear during the discussions of the Committee and its advisers that several adverse effects of steroidal contraception appear to be due to their content of oestrogen. For this reason, the Committee believes that it is wise to use low-dosage oestrogen formulations when possible. The Committee hopes that work on steroidal contraceptives containing progestagens alone will be continued and expanded.

The Committee recognizes that the availability of medical personnel differs widely in different parts of the world. In areas where there is a shortage of doctors,

the distribution of steroidal contraceptives by paramedical personnel under medical supervision may free the physician's services for more demanding and urgent tasks.

There is no doubt that steroidal contraception is widely used and is an effective method of family planning. However, the Committee emphasizes that steroidal contraception is only one of several family planning procedures. Various methods may be applicable under differing circumstances or at different periods throughout a woman's reproductive life.

The Committee recognizes that, while any innovation in medicine carries with it certain risks which are by their nature unpredictable, the availability and use of steroidal contraceptives is an important factor in maternal health and in the health of the family. The Committee feels, as a result of its deliberations, that the continued use of steroidal contraception is fully justified. The possible risks must be weighed against the probable benefits. In evaluating the suitability of different methods of contraception, relative effectiveness is significant.

APPENDIX B

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